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Harold E. Varmus, MD
Director, National Institutes of Health
Building 1, Room 126
1 Center Drive, MSC 0 148
Bethesda, MD 20892-0148

Dear Dr. Varmus:

Thank you for your letter concerning a speech made by our Acting Deputy Commissioner, Lawrence J. Goffney, Jr., at the annual meeting of the American Association for the Advancement of Science, regarding the patentability of Expressed Sequence Tags (ESTs).

I truly understand your concern regarding the perceived change in our policy and the impact that this has had an the investment and scientific communities We are also aware of the considerable media attention these comments have produced and clearly understand the issues at the heart of this controversy. You can be assured that our policy regarding the patentability of small fragments of RNA and DNA, including ESTs, has not changed.

To address your concerns and briefly those expressed by Dr. Spiegel in his letter to Mr. Goffney; an EST rimy be patentable in the United States under appropriate circumstances (i.e., an EST, which meets all the criteria under applicable patent laws, including utility, enablement, novelty, and unobviousness). Mere allegation of the utility of an EST as a probe without further disclosure is not sufficient to meet the utility and enablement criteria. Example 9, in our training materials for the Patent Utility Guidelines, outlines a DNA probe which lacks utility because no utility for the protein corresponding to the cDNA identified by the probe or for the cDNA itself, was disclosed. A copy of Example 9, setting forth the Patent Utility Guidelines, has been enclosed for your convenience.

The patentability of any EST application is meticulously analyzed to determine the sufficiency of the disclosure and the enabled utilities for the EST. For example, disclosures of the use of ESTs for forensic identification, tissue type or origin identification, chromosome mapping, chromosome identification, and to tag a gene of known and useful function, may be enabled if supported by a sufficient disclosure. Examples of potentially non-enabled utilities include location of disease-associated genes, wherein the disease has no known genetic origin; use as an anti-sense reagent, wherein the corresponding protein to be suppressed is unknown; use as a triplex probe to inhibit expression of a protein, where the protein and its function are unknown; and, for location and identification of genes of unknown utility.

Patent claims limited in scope to a specific novel and non-obvious EST, generally should not preclude the future patenting of the corresponding, latter discovered, full length gene of known function or of therapeutic technologies arising therefrom. Under appropriate and limited circumstances, claims of a perceived broad scope that are adequately supported by the disclosure

under 35 USC 112 and the state of the art may be patentable, but such claims do not necessarily preclude future patenting of the full length gene.

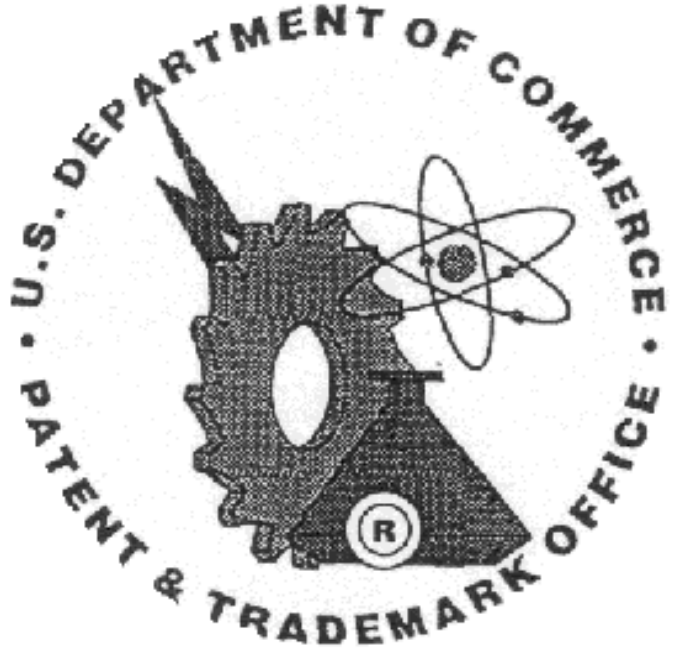
We are continuously working with the biotechnology and investment communities to ensure that the patent system fulfills its constitutional mandate while enhancing the well-being and health of our Nation.

Again, thank you for informing me of your concerns and, as always, I welcome your comments and suggestions for improving and maintaining the public service of the Patent and Trademark Office,

Sincerely,

/s/
Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

Enclosure



35 U S C §101 Utility Guidelines

Training Manual

August 22, 1995

Example 9: DNA Fragments

Specification: The specification discloses 4332 nucleic acid sequences that were obtained from a human cDNA library that was formed using human epithelial cells. The sequences, SEQ. ID. NOS. 1-4332, are believed by applicant to be fragments of full length genes. Thus, it is clear that all of the sequences comprise at least part of the coding sequence for a protein that actually produced in the human cells. The specification discloses how to use each of the 4332 nucleic acid sequences as a probe to obtain the full length gene that corresponds to the nucleic acid sequence, which full length gene can be used to recombinantly make the corresponding protein, which can then be used to study the cellular mechanisms and activities in which the protein is involved. There is a generic disclosure of how to recombinantly make the corresponding protein from each of the sequences. The sequences vary in length but include sequences long enough to encode functional proteins, i.e. these could be genes. There is one fully explained example of using SEQ. ID. NO. 22 to obtain the corresponding gene which is then used to produce the corresponding protein which was isolated and purified but has no known biological activity and was only characterized by its sequence. Thus, no use is disclosed for the protein other than the possibility of using it to study the cellular mechanisms and activities in which the protein is involved.

Claims: There are 4332 claims in the application with each claim reciting --A cDNA molecule consisting of the sequence set forth in SEQ. ID. NO. X.-- where X is also the claim number.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? The specification as filed does not disclose or provide any evidence that points to an activity for the cDNA molecules or the proteins which can be obtained using the cDNA molecules such that another non-asserted utility would be well established, Additionally, there is no art of record that discloses or provides any evidence that points to an activity for the cDNA molecules or the proteins which can be obtained using the cDNA molecules such that another non-asserted utility would be well established. Consequently, the answer to the question is no.

2) Has the applicant made any assertion of utility for the specifically claimed invention? Here, there is an asserted utility, i.e., each claimed cDNA molecule can be used as a probe to obtain the full length gene that corresponds to the cDNA molecule, which full length gene can be used to recombinantly make the corresponding protein, which can then be used to study the cellular mechanisms and activities in- which the- protein is involved.

3) Is the asserted utility specific? The answer to this question would be no. As seen in 2) above, the asserted utility for the claimed cDNAs is a method of making the corresponding protein. Thus, to determine whether or not this method is a "specific utility", it must be determined whether or not the product, i.e., the corresponding protein, has a "specific utility". Here, the only utility asserted for the protein is studying the properties of the protein itself or the mechanisms in which the protein is involved. This clearly does not define a

“real world" context of use. Since the asserted utility for the protein (studying the properties of the protein itself or the mechanisms in which the protein is involved) does not define a "real world" context of use, a method of making that protein (the utility for the claimed cDNAs) also could not define a "real world" context of use. In fact, both utilities clearly would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use.

Thus, the conclusion that can be reached from this analysis is that both a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should be made.

Examiner's Rejection

Claims 1-4332 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claimed cDNA compounds are not supported by a specific asserted utility because the specification states only that the cDNA compounds are useful as probes for assisting in -the isolation of full-length DNA compounds (i.e., genes), which full-length DNA would be used to make protein. Once the protein is obtained, the protein would be used in conducting research to functionally characterize the protein. A starting material which can only be used to produce a final product does not have a specific asserted utility in those instances where the final product is not supported by a specific utility. In this case the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have no asserted or otherwise identified

specific utility. The research contemplated by Applicants to establish utility for potential protein products by elucidating the properties, especially the biological activities, of the proteins has not been specified and does not constitute a specific utility. Note, because the claimed invention is not supported by a specific asserted utility for the reasons set forth above, credibility cannot be assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claims 1-4332 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

POINTS OF AGREEMENT

No.	Utility	Utility Enabled?	Remarks
1	Location of Disease Associated Genes	No	Do not always know whether a given disease has a genetic origin or association. No guidance as to where to start. For example, if one knows a disease causing gene is on the short arm of chromosome 13, there is no clue as to which (if any) EST would be useful.
2	Antisense Reagents	No	Since one does not know which proteins the ESTs are associated with, one does not know which protein might be reduced as a result of an antisense reagent. There are other difficulties in antisense therapy for any given antisense reagent that would result in undue experimentation for one of skill in the art to use the ESTs as antisense agents.
3	Triplex Probe	No	Triplex probe used to inhibit the expression of a protein is not enabled because one has no clue as to which protein would be decreased or what its function might be. Same as #2 above.
4	Protein Production, Proteins per se, etc.		See #2 above.
5	Antibody Production, etc.	No	Since one does not know the protein encoded by any given EST or any antigenic properties of such proteins, one of skill in the art would need to perform undue experimentation to produce antibodies to the proteins.

POINTS OF DISAGREEMENT

No.	Utility	Utility Enabled?	Remarks
1	Chromosome Identification	Yes	Any one of three methods mentioned in the specification could be used by one of skill in the art to identify chromosomes (i.e. determine the chromosomal origin of the sequence information is a given EST) without undue experimentation. These are: (1) PCR using EST informed primers against DNA from somatic cell hybrids containing a single human chromosome, (2) PCR using EST informed primers against flow-sorted human chromosomes, and (3) FISH (Fluorescence In Situ Hybridization) using the entire cDNA insert from a clone corresponding to any given EST.
2	Chromosome Mapping	Yes	Chromosome mapping could be done similar to the determination of chromosomal origin on somatic cell hybrids that contain only fragments of human chromosomes or by FISH as in #1 above.
3	Human Identification and Forensic Identification	Yes	PCR informed primers can be used against a sample of undetermined origin. A plurality of PCR reactions are run separately and the PCR products are sequenced (all routine work). The same primers are used against DNA from a known individual human source and the sequences are compared. If there are any differences, the undetermined DNA source is not the same as the known source. As more sequences are determined to be the same, the probability of the two sources being the same increases. The precise mathematical relationship between sequence identity and probability of source identity is still an open question, but is of no relevance to the enablement issue here because it is a concern about interpretation of data that those of skill in the art can obtain using the instant application and the level of skill in the art at the time the application was filed.
4	Identification of Tissue Type or Origin	Yes	This can be done by amplification using EST informed PCR primers against either mRNA from a given tissue sample or a cDNA library derived from a given tissue sample and scoring by a simple plus/minus assay for a random collection of primers.